CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-669

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 6

2. ANDA # 75-669

3. NAME AND ADDRESS OF APPLICANT
Faulding Pharmaceutical Co.
Attention: Kala Patel, M.S., R.PL.
11 Commerce Drive
Cranford, NJ 07016

4. BASIS OF SUBMISSION
Reference Listed drug product: Pepcid^{R} Injection (Preservative-free) by Merck approved in NDA #19-510.

The firm filed a Paragraph III patent certification. The patent (#4,283,408) expires 10/15/00.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Famotidine Injection, Single Dose vial

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 7-9-99
Acknowledgement: 8-4-99
FDA Deficiency Letter: 2-1-00
Amendment Response: 2-10-00
New Correspondence to Amendment: 5-31-00
Fax Deficiency Letter: 6-16-00
Response to Fax: 6-30-00
Minor Deficiency Letter: 8-25-00
Response to Minor: 9-21-00
Minor Deficiency Letter: 10-18-00
Amendment: 10-25-00
T-con: 11-17-00
T-amendment: 11-17-00

Tentative Approval: 12-12-00
Minor amendment to TA: 1-17-01

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

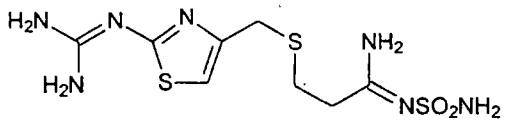
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Injection, IV

14. POTENCY
10 mg/mL - Single Dose Vial

15. CHEMICAL NAME AND STRUCTURE

Generic name: Famotidine
Chemical name: Propanimidamide, *N*'-(aminosulfonyl)-3-[[[2-[(diaminoethylene)amino]-4-thiazolyl]methyl]thio]-
Chemical formula: $C_8H_{15}N_7O_2S_3$
Molecular weight: 337.45
CAS number: 76824-35-6
Pharmacological category: Antagonist (to histamine H2 receptors)
Chemical structure:



16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry remains adequate. No CMC changes since the TA was granted on December 12, 2000. Famocyamidine is not monitored in the drug product.
Bioequivalence is acceptable (waiver granted) by H.Nguyen on 8/23/99.
Labeling is acceptable as of 11/21/00 by K.Lee.
Microbiology is acceptable 10/23/00 by PDeleo.
EER is acceptable 8/6/99.
Methods sent to Phila-DO 12/6/99. Acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is fully approvable.

19. REVIEWER: DATE COMPLETED:
Karen A. Bernard, Ph.D. 2-26-01

OCT 18 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-669 APPLICANT: Faulding Pharmaceutical Co.

DRUG PRODUCT: Famotidine Injection, 10 mg/mL Single Dose Vial

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

At this time, you are requested to address the following issues regarding your intended drug substance supplier:

ıas proposed a new acceptance criteria and method of quantitation for the process impurity in the drug substance. At this time we recommend that you contact nd then submit a revised Certificate of Analysis along with an analytical method for the control of the impurity.

In addition, since you are also monitoring this impurity in your drug product, we ask that you provide a commitment that the drug substance that you intend to use for future production batches of the drug product will also meet the new acceptance criteria established.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG 25 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-669 APPLICANT: Faulding Pharmaceutical Co.

DRUG PRODUCT: Famotidine Injection, 10 mg/mL Single Dose Vial

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. Please be advised that this application cannot be approved until deficiencies regarding DMF ıave been satisfactorily addressed by the DMF holder. Please do not respond until you have been informed that the DMF holder has responded to the deficiencies.

Sincerely yours,

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 16 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-669 APPLICANT: Faulding Pharmaceuttical Co.

DRUG PRODUCT: Famotidine Injection, 10 mg/mL Single Dose Vial

The deficiencies presented below represent FAX deficiencies.

Deficiencies:

1. Your response concerning the holding periods for the manufacture of this product require clarification. In your response you stated that an cime limit on the processing time for Famotidine Injection was assigned in the exhibit batch records. You have also stated that the time limit will be validated during production of the first three process validation batches. Although it is clear that the drug product manufacture will be validated in all respects, it is unclear if you have actually assigned a holding period pre-approval not post approval for this product. You are requested to clearly establish and assign a reasonable production time limit/ holding period for the manufacture of the Famotidine Injection prior to approval and not during validation. If a change must be made to the assigned holding time, you are required to make the appropriate post approval change to the application.

2. You have also submitted a copy of the in-process bioburden results for the exhibit batch in your response to this issue. We note that the referenced data (page 396) is under a section entitled "In-Process Specifications and Test Results for Famotidine Injection 10 mg/mL Batch #98S008". This material was already reviewed and is not the information that was requested. You should have included a section of all in-process testing specifications for the manufacture of **future** batches of Famotidine Injection. The presentation of exhibit batch data does not necessarily suggest that these are the proposed future specifications. For full clarification purposes, you are requested to provide a listing of all future in-process testing specifications you intend to implement for this product.

3. The Phila-DO did perform methods validation on the drug product analytical methods you submitted. Based on the field review of the methods you are requested to address the following comment:

   In the Determination of Related Compounds test, a Resolution requirement should be included with the system

suitability. The RRF values specified in the method differs from the calculation made with the data submitted in page 356 of the Method Validation package submitted with ANDA 75-669 (header/footer read "Protocol No.: 99-053-P, Method Number 8108/Page 16 of 40". The Blank Chromatogram was the other runs to correct a baseline drift problem.

4. It was also noted in your 5/31/00 amendment, that the Assay specification on release reads , although the original finished product specifications (page 498), showed as the Assay specification. This should also be clarified. If the specification has been changed it should also have been noted in your 5/31/00 amendment in addition to the Description revision.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-669 APPLICANT: Faulding Inc.

DRUG PRODUCT: Famotidine Injection, 10 mg/mL Single Dose Vial

The deficiencies presented below represent MAJOR deficiencies.

Deficiencies:

1. You are requested to provide a list of excipient functionalities for each of the ingredients in the formulation.

2. We also recommend that you establish a Microbial and Fungal count specification on the Famotidine raw material.

3. We note that since your testing for Nitrogen meets USP 23 and NF standards, we suggest that you include a NF designation after Nitrogen and include Nitrogen, NF in your Components and Composition statement. Also, since you are using Nitrogen in the gaseous state, it is unclear why you use "Liquid Nitrogen" in your Component description section.

4. It is noted that a pH check is performed during the manufacturing process, although it does not appear that any pH adjustment is made to the bulk solution. Please provide an explanation as to what occurs if the pH is not met during the manufacturing in-process check.

5. The batch records indicate that the first step in the compounding procedure involves addition of to the mixing tank. You should establish a clear temperature limit for and include this in the batch records.

6. In accordance with 21 CFR, please clarify if you have established any time limits on production, specifically with respect to holding periods for the bulk solution prior to filling.

7. A visual in-process clarity check is made on the bulk solution, however, no limit except visual check for particles is established. Since Famotidine is only very slightly soluble in water, it is recommended that a clear and measurable limit be established for this in-process clarity check to provide assurance that the product is indeed in solution.

8. We also note that you will perform Osmolality testing on the bulk solution in-process, however, there does not appear to be

any specification listed for this test. An in-process specification for this test is recommended.

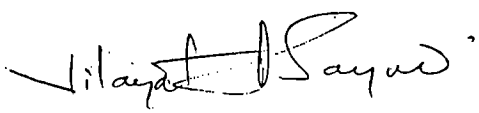
9. We also note that you state that you will perform "routine bioburden testing on the bulk solution", however no specification was listed. Please provide the in-process specification you intend to use for all future bulk bioburden testing.

10. Please comment if you have performed testing for Oxygen in Headspace for this product. This is recommended.

11. The data provided for lot #98S008 on release do not support the high levels of related substances proposed for the finished product specifications.

12. You should provide the Limit of Detection (LOD) and Limit of Quantitation (LOQ) for the Assay method used for the Famotidine Injection. This information does not appear to be in the method validation package.

Sincerely yours,



Florence S. Fang
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